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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/601,305	06/19/2003	Mark Zylka	CALTE.015A	5172

20995 7590 10/25/2006

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EXAMINER	
YAO, LEI	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 10/25/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/601,305	ZYLKA ET AL.	
	Examiner	Art Unit	
	Lei Yao, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 July 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-22* is/are pending in the application.

4a) Of the above claim(s) *9-10, 12-16* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8,11 and 17-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *6/19/03* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *2/9/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election of group I in the reply filed on 7/26/06 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 1-22 are pending. Claims 9-10, 12-16 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Claims 1-8, 11, and 17-22, drawn to diagnosing a skin cancer comprising determining the cell expressing MrgX2 protein (SEQ ID NO: 4) with antibody, are examined on merits.

Priority

This application claims benefit of U.S. provisional application No. 60/391127, filed on 6/21/02, which is acknowledged.

Information Disclosure Statement

The information disclosure statement (s) (IDS) submitted on 2/9/04 are/is considered by the examiner and initialed copies/copy of the PTO-1449 are/is enclosed.

Objection of Drawing

Figures 3, 4, and 5 are objected to. It is not clear that the pictures represent the expression of mMrgB1 or MrgB1 protein detected by antibody or expression of mRNA detected by nucleic acid probe in figures 3 and 4. It is not clear what WM1552C, WM3208, and WM278, etc stand for, melanoma, normal skin cells or control cells in figure 5. Further explanations in the drawing or figure legends are required for examination.

Claim Rejections - 35 USC § 101/112

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1-8, 11, and 17-22 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific, substantial, and credible asserted utility or a well established utility.

Claims are drawn to a method of diagnosing skin cancer comprising melanoma by detecting the expression of MrgX2 protein (SEQ ID NO: 4) in the tissue or cell samples, where in the MrgX2 expression is determined by contacting the tissue sample with an antibody comprising labeled monoclonal antibody that specifically binds to the tissue sample or by contacting the an antibody to the protein isolated from tissue sample.

In order to fulfill the requirements of 35 U.S.C. 101, said binding must be indicative of a specific, substantial and credible utility, such as the diagnosis of a pathological condition. The specification teaches MrgX2 protein comprising amino acid sequence SEQ ID NO: 4 (para 13). The specification teaches antibody to MrgX2 protein (page 12-13). The specification teaches that MrgX2 RNA is exclusively expressed in melanoma cell lines, not in other tissues (table 2, page 45 and figure 5). Although the specification teach a general method used in the art for diagnosing melanoma by antibodies to human MrgX2 protein, the specification does not teach whether the levels of MrgX2 protein, as opposed to the polynucleotides (RNA) encoding said protein, in the melanoma cells or tissues samples are higher than normal skin tissues. The specification does not provide any objective evidence on the expression of MrgX2 protein in either melanoma tissue, melanoma cell, or any normal tissues samples. The specification teaches neither the expression of MrgX2 protein (SEQ ID NO: 4) by any primary or invasive/metastasis melanoma cells, nor binding of an antibody to melanoma cells, which express MrgX2 protein.

Therefore, the specification only provides an evidence of the expression of MrgX2 in the melanoma and normal samples by showing the levels of the message RNA (mRNA). The specification does not provide any teaching on whether the protein expression is correlated with the levels of mRNA in any of these tissues or cells. The art recognizes that expression of mRNA neither dictate nor predict the

translation of such mRNA into a polypeptide. For examples, the abstract of Brennan et al., (Journal of Autoimmunity, 1989, vol. 2 suppl., pp. 177-186) teaches that high levels of the mRNA for TNF alpha were produced in synovial cells, but that levels of the TNF alpha protein were undetectable. The abstract of Zimmer (Cell Motility and the Cytoskeleton, 1991, vol. 20, pp. 325-337) teaches that there is no correlation between the mRNA level of calcium-modulated protein S100 alpha and the protein level, indicating that S100 protein is post-transcriptionally regulated. The abstract of Powell et al., (Pharmacogenetics, 1998, Vol. 8, pp. 411-421) teaches that mRNA levels for cytochrome P450 E1 did not correlate with the level of corresponding protein, and conclude that the regulation of said protein is highly complex. In this event although the mRNA of MrgX2 was demonstrated to be expressed in melanoma, according the teachings in the art, said demonstration cannot be relied upon to anticipate that MrgX2 protein of SEQ ID NO: 4 would be similarly expressed in same cancer cells.

More evidence abounds in which protein levels do not correlate with steady-state mRNA levels or alterations in mRNA levels are following: The abstract of Hell et al., (Laboratory Investigation, 1995, Vol. 73, pp. 492-496) teaches that cells in all types of Hodgkin's disease exhibited high levels of bcl-2 mRNA, while the expression of the Bcl-2 protein was not homogenous to said cells. The abstract of Carrere et al., (Gut, 1999, vol. 44, pp. 545-551) teaches an absence of correlation between protein and mRNA levels for the Reg protein. The abstract of Guo et al., (Journal of Pharmacology and Experimental Therapeutics, 2002, vol. 300, pp. 206-212) teaches that Oatp2 mRNA levels did not show a correlation with Oatp2 protein levels, suggesting that regulation of the Oatp2 protein occurs at both transcriptional and post-translational level. These references serve to demonstrate that levels polynucleotide transcripts cannot be relied upon to anticipate levels of protein expression. Further, the abstract of Jang et al., (Clinical and Experimental Metastasis, 1997, vol. 15, pp. 469-483) teaches that further studies are necessary to determine if changes in protein levels track with changes in mRNA levels for metastasis associated genes in murine tumor cells, thus providing further evidence that one of skill in the art cannot anticipate that the level of a specific mRNA expressed by a cell will be paralleled at the protein level due to complex homeostatic factors controlling translation and post-translational modification. Thus,

predictability of protein translation is not necessarily contingent on mRNA expression due to the multitude of homeostatic factors affecting transcription and translation.

Since there is not evidence showing the expression of MrgX2 protein (SEQ ID NO: 4) in melanoma tissue or cells, the antibody to the protein would not bind to the melanoma tissue or cells, which express only mRNA of MrgX2. Since the specification has not correlated the claimed method of binding an antibody to a melanoma tissue or cells with the expression of mRNA in (not a protein) in the cells, instant method claims recite diagnosing a skin cancer including melanoma in a patient comprising determining the levels of expressing MrgX2 protein (SEQ ID NO:4) by binding an antibody to human melanoma tissues, cells or proteins isolated from the tissues do not meet the requirement of 35 U.S.C. 101.

If a molecule is to be used as a surrogate for a disease state some specific disease state must be identified in some way with the polynucleotide or polypeptide encoded there from. There must be some expression pattern or evidence of altered form that would allow the claimed polypeptides or polynucleotides to be used in a diagnostic manner. Many proteins are expressed in normal tissues and diseased tissues. Therefore, one skilled in the art needs to know that the MrgX2 protein is present only in diseased tissue to the exclusion of normal tissue or present in diseased tissue at higher levels or in a different form from that present in normal tissues. However, in the absence of any disclosed relationship between the protein expression and pathological condition, any information obtained in an effort to establish a differential expression pattern would constitute further research on establishing a specific, substantial, and credible utility for the method reliant on the presence of the MrgX2 protein in melanoma tissue or cells. "Congress intended that no patent be granted on a chemical compound whose sole 'utility' consists of its potential role as an object of use-testing". Therefore, without objective evidence that the binding of an antibody to MrgX2 protein (SEQ ID NO: 4) expressed on melanoma tissue or cell is indicative of some skin cancerous condition, the instant claims lack a specific, substantial, and credible asserted utility.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-8, 11, and 17-22 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific, substantial, and credible asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Conclusion

No claims are allowed.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

1. Burmer et al., (WO02/061087, International filing date, 12/19/01) disclose G-coupled receptors comprising MrgX2 protein (SEQ ID NO: 4) and antibodies to the receptors. Burmer et al., also disclose a general method of diagnosing diseases and cancers comprising melanoma with the antibodies to the antigenic receptor specifically expressed on the cells or tissues. Burmer et al., do not explicitly and specifically teach or suggest a method of diagnosing a skin cancer or melanoma by determining the levels of MrgX2 protein (SEQ ID NO: 4) expressed by the melanoma cell or tissues.

2. Wolf et al., (US Patent Application Publication, 2002/0116724, effective filing date, 8/31/2000) disclose G-coupled receptors comprising MrgX2 protein (SEQ ID NO: 4) and antibodies to the receptors. Wolf et al., disclose that abnormal expression of MrgX2 protein is involved in skin disorder, such as wound healing. Wolf et al., also disclose a method of diagnosing skin disorder resulted from the abnormal expression of the receptors. Burmer et al., do not teach or suggest a method of diagnosing a skin cancer or melanoma by determining the levels of MrgX2 protein (SEQ ID NO: 4).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lei Yao, Ph.D. whose telephone number is 571-272-3112. The examiner can normally be reached on 8am-6.00pm Monday-Thursday.

Any inquiry of a general nature, matching or file papers or relating to the status of this application or proceeding should be directed to Kim Downing for Art Unit 1642 whose telephone number is 571-272-0521

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Lei Yao, Ph.D.
Examiner
Art Unit 1642

LY

JEFFREY SIEW
SUPERVISORY PATENT EXAMINER